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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/054,638	01/22/2002	Robert P. Ryall	01-059-A	9398

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EXAMINER
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ART UNIT	PAPER NUMBER
1645	11

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
10/054,638	Robert
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jan 27, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-8 and 10-16* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-8 and 10-16* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election

1) Acknowledgment is made of Applicant's election filed 01/27/03 (paper no.10) of invention I, claims 1-8 and 10-16, in response to the restriction requirement mailed 10/28/02 (paper no. 5). It is noted that Applicant has canceled claims 9 and 17.

Status of Claims

2) Claims 9 and 17 have been canceled via the response filed 01/27/03.

Claims 1-8 and 10-16 are pending and are under examination.

Priority

3) This application claims domestic priority to the provisional application, SN 60/263,435, filed 01/23/2001.

Rejection(s) under 35 U.S.C. § 101

4) Claims 1 and 10, and claims dependent therefrom, are rejected under 35 U.S.C. § 101 as being directed to a non-statutory subject matter. The claims read on products of nature, i.e., naturally occurring bacterial mixture of two serogroups of *Neisseria meningitidis* that contain non-isolated capsular polysaccharides naturally conjugated to one or more proteins on the bacterial surface. Claims 1 and 10 lack limitations which distinguish the products from those that may exist naturally. Consequently, the claims do not embody patentable subject matter as defined in 35 U.S.C § 101. See MPEP 2105. It is suggested that Applicant use a limitation, such as, --isolated-- or --purified-- in connection with the capsular polysaccharide and the carrier protein in the claimed product to reflect the hands of the inventors in the production or creation of the recited product as is supported, for instance, in Example 3 of the instant specification.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

5) Claims 1-8 and 10-16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

(a) The product claims 11-16 are indefinite and/or confusing in their direct or indirect dependency from a canceled method claim, i.e., claim 9. It is suggested that Applicant change the claim dependency from claim 9 to --claim 10--.

(b) Claim 2 has improper antecedence in the recitation "**the** capsular polysaccharides" [Emphasis added]. Claim 2 depends from claim 1, which recites 'a capsular polysaccharide', but not 'capsular polysaccharides'.

(c) Claim 1 is incorrect in the recitation '**a** capsular polysaccharide from two or more serogroups', because two or more serogroups would have two or more distinct capsular -- polysaccharides-- as opposed to "a"capsular polysaccharide.

(d) Claims 7 and 8 have improper antecedence in the recitation "of claim 5, wherein **the** adjuvant" [Emphasis added]. Claims 7 and 8 depend from claim 5, which does not recite any adjuvant. It is suggested that Applicant change the dependency of claims 7 and 8 from claim 5 to --claim 6--.

(e) Claims 15 and 16 have improper antecedence in the recitation "of claim 13, wherein **the** adjuvant" [Emphasis added]. Claims 15 and 16 depend from claim 13, which does not recite any adjuvant. It is suggested that Applicant change the dependency of claims 15 and 16 from claim 13 to --claim 14--.

(f) Claims 3-6, which depend directly or indirectly from a base claim identified above, are also rejected as being indefinite because of the vagueness or indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. § 102

6) The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> **(b)** the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7) Claims 1-3, 5-7, 10, 11 and 13-15 are rejected under 35 U.S.C. § 102(b) as being anticipated by Costantino *et al.* (*Vaccine* 10: 691-698, 1992), Lieberman *et al.* (*JAMA* 275: 1499-1503, 1996), or Twumasi *et al.* (*J. Infect. Dis.* 171: 632-638, 1995).

It is noted that depolymerized polysaccharides, i.e., oligosaccharides, are included as preferred embodiments in the scope of the claimed composition. See sections [0024] and [0025] of the instant specification.

Claims 11 and 13-15 are included and claim 9 is excluded in this rejection on the assumption

that claims 11 and 13-15 depend, directly or indirectly, from claim 10, as opposed to claim 9. Similarly, claims 7 and 15 are included in this rejection on the assumption that these claims depend from claims 6 and 14 respectively, as opposed to claims 5 and 13 respectively.

Costantino *et al.* taught an immunogenically effective amount of a CRM 197-meningococcal A and C conjugate vaccine (i.e., multivalent vaccine) comprising hydrolyzed serogroup A and C meningococcal capsular polysaccharides conjugated to CRM 197 diphtheria toxoid and aluminum hydroxide (i.e., adjuvant). See abstract; 'Materials and Methods'; 'Results'; Figure 1; and footnotes to Figures 5 and 6.

Lieberman *et al.* disclosed an immunogenically effective amount of a combination meningococcal conjugate vaccine (i.e., multivalent vaccine) comprising depolymerized capsular polysaccharides from groups A and C *N. meningitidis* conjugated to the protein carrier, CRM_{197}, the non-toxic diphtheria toxin mutant. The conjugate vaccine is contained in aluminum hydroxide adjuvant (see under the section 'Vaccines' on page 1500).

Twumasi *et al.* taught an immunogenically effective amount of a group A plus group C meningococcal polysaccharide-CRM_{197} conjugate vaccine (i.e., multivalent vaccine). The conjugate vaccine is contained in aluminum hydroxide adjuvant (see under the section 'Vaccines' on page 1500).

Claims 1-3, 5-7, 10, 11 and 13-15 are anticipated by Costantino *et al.* or Lieberman *et al.* or Twumasi *et al.*

8) Claims 1-3, 5-7, 10, 11 and 13-15 are rejected under 35 U.S.C. § 102(b) as being anticipated by Granoff (WO 98/58670).

It is noted that depolymerized polysaccharides, i.e., oligosaccharides, are included as preferred embodiments in the scope of the claimed composition. See sections [0024] and [0025] of the instant specification.

Claims 11 and 13-15 are included and claim 9 is excluded in this rejection on the assumption that claims 11 and 13-15 depend, directly or indirectly, from claim 10, as opposed to claim 9. Similarly, claims 7 and 15 are included in this rejection on the assumption that these claims depend from claims 6 and 14 respectively, as opposed to claims 5 and 13 respectively.

Granoff disclosed a polyvalent (i.e., multivalent) meningococcal vaccine comprising

immunologically effective amounts of two or three protein-polysaccharide conjugates containing meningococcal capsular polysaccharide antigen from more than one meningococcal species conjugated to an appropriate carrier molecule, such as, the non-toxic diphtheria toxin mutant, CRM_{197} (see page 11, second paragraph; and first half of page 12). In one embodiment, the composition is the art-known meningococcal A and C oligosaccharide-based glycoconjugate vaccine, or the trivalent meningococcal A, B and C oligosaccharide-based glycoconjugate (see last paragraph on page 12). Granoff disclosed a bivalent meningococcal serogroup A and C oligosaccharide-protein conjugate vaccine wherein meningococcal serogroup A and C oligosaccharides are conjugated to the non-toxic diphtheria toxin mutant, CRM_{197}, and the antibody responses elicited by the vaccine. The vaccine is contained in aluminum hydroxide adjuvant (see page 19; and Figure 1).

Claims 1-3, 5-7, 10, 11 and 13-15 are anticipated by Granoff.

Rejection(s) under 35 U.S.C. 103

9) The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person. having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 148 USPQ 459, that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or unobviousness.

10) Claims 1, 6, 8, 10, 14 and 16 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Granoff (WO 98/58670).

Claims 8 and 16 are included and claims 5 and 13 are excluded in this rejection in this rejection on the assumption that these claims depend, from claims 6 and 14 respectively, as opposed to claims 5 and 13 respectively.

The teachings of Granoff are explained above, which do not disclose the use of aluminum phosphate in conjugate vaccine.

However, it is very routine and conventional in the art of vaccines to use an alternative, art-known aluminum-based adjuvant, such as, aluminum phosphate. In fact, Granoff taught that aluminum phosphate can be added as an adjuvant to his conjugate vaccine composition (see page 15, first 8 lines).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the art-known aluminum phosphate as the adjuvant in place of aluminum hydroxide in Granoff's bivalent conjugate vaccine comprising meningococcal serogroup A and C oligosaccharides conjugated to CRM_{197}, to produce the instant invention with a reasonable expectation of success, because Granoff taught that it was routine and conventional to use an alternative aluminum-based adjuvant, such as, aluminum phosphate along with his conjugate vaccine. Substitution of one aluminum adjuvant with an alternate art-known aluminum adjuvant is well within the realm of routine experimentation and would have expected to yield similar, if not better, results or effects.

Claims 1, 6, 8, 10, 14 and 16 are *prima facie* obvious over the prior art of record.

11) Claims 1, 4, 10 and 12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Granoff (WO 98/58670).

Claim 12 is included and claim 9 is excluded in this rejection on the assumption that claim 12 depends, from claim 10, as opposed to claim 9.

The teachings of Granoff are explained above, which do not expressly disclose a multivalent meningococcal conjugate vaccine wherein the serogroup A, C, W-135 and Y meningococcal capsular polysaccharides are conjugated to one or more carrier proteins.

However, Granoff did teach immunologically effective amounts of a U.S.-licensed quadravalent or tetravalent meningococcal Menomune® polysaccharide vaccine comprising serogroups A, C, Y and W135 meningococcal capsular polysaccharides (see page 18; second paragraph on page 6; and first paragraph on page 20). Granoff expressly taught the disadvantages of meningococcal polysaccharide vaccines, including that of the tetravalent A, C, Y and W135 meningococcal Menomune® polysaccharide vaccine, in the statement that: a) they are poorly

immunogenic in infants less than 2 years of age, the age group at greatest risk of developing meningococcal disease; b) they do not provide long-lasting protection in older children and adults; and that they induce immunological paralysis of toddlers and adults to meningococcal polysaccharides; and c) they induce immunologic tolerance in infants less than 6 months of age (see the first half of page 3; last half of page 9; and lines 4-10 of page 10). Granoff explicitly taught that anti-meningococcal conjugate vaccines are more effective than unconjugated polysaccharide vaccines in infants and toddlers (see lines 1-4 on page 4). Granoff taught his unexpected discovery that an anti-meningococcal conjugate vaccine composition in adults, as opposed to an unconjugated anti-meningococcal polysaccharide vaccine, induces polysaccharide-responsive memory B cells, long-term immunologic memory and a readily boostable response in vaccinated subjects, both of which factors contribute to more robust and durable protection against meningococcal disease (see first full paragraph on page 9).

Given the art-recognized various disadvantages of the U.S.-licensed quadravalent or tetravalent meningococcal Menomune® polysaccharide vaccine comprising serogroup A, C, Y and W135 meningococcal capsular polysaccharides as taught by Granoff, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to conjugate the serogroup A, C, Y and W135 meningococcal capsular polysaccharides present in the Menomune® polysaccharide vaccine disclosed by Granoff to the art-known protein carrier, non-toxic diphtheria toxin mutant, CRM_{197}, to produce the instant invention with a reasonable expectation of success. One of skill in the art would have been motivated to produce the instant invention for the expected benefit of: a) rendering the tetravalent meningococcal Menomune® unconjugated polysaccharide vaccine advantageously more effective in infants and toddlers who are at greatest risk of developing meningococcal disease, and rendering it capable of inducing polysaccharide-responsive memory B cells, long-term immunologic memory, a readily boostable response in vaccinated subjects, and a more robust and durable protection against meningococcal disease as expressly taught by Granoff; and b) avoiding the undesirable immunological paralysis of toddlers and adults to meningococcal polysaccharides and avaoiding immunologic tolerance in infants less than 6 months of age as expressly taught by Granoff.

Claims 1, 4, 10 and 12 are *prima facie* obvious over the prior art of record.

Objection(s)

12) Claims 1, 2 and 16 are objected to for the following reasons:

(a) Claim 16 is objected for the recitation "the" instead of --The– at the beginning of claim 16.

(b) Claim 2 is objected to for lacking a period at the end of the claim.

(c) Claim 1 is objected to for the grammatically incorrect recitation "one or more a carrier protein(s)".

Remarks

13) Claims 1-8 and 10-16 stand rejected.

14) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

15) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

S. DEVI, PH.D.
PRIMARY EXAMINER

April, 2003